Faculty Profile

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Katrina Miranda

Associate Professor

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Honors

- NSF CAREER Award, 2007
- Presidential Early Career Award for Scientists and Engineers (PECASE), 2008
- Achievement Award for Outstanding Mentor of Graduate/Professional Students (GPS), GPS Council, 2010

Education and Appointments

- B.S. 1989, Northern Arizona University
- Ph.D. 1996, University of California, Santa Barbara
- Postdoctoral Fellow 1996-1998, Department of Cell Biology and Physiology, University of New Mexico
- Cancer Research Fellow 1998-2002, National Cancer Institute, NIH (Dr. David A. Wink)

Research Interests

- Inorganic
- Bioinorganic
- Chemical Biology
- Spectroscopy/molecular Structure
- Synthesis/Synthetic Methods Development

Research Summary

Chemical Biology of Nitrogen Oxides; New Detection Techniques and Donors of Nitrogen Oxides; Drug Development

Nitric oxide (NO), which is synthesized in the body via enzymatic oxidation of L-arginine, is critical to numerous physiological functions but also can contribute to the severity of diseases such as cancer or pathophysiological conditions such as stroke. This diversity in the responses to NO biosynthesis is a reflection of the diverse chemistry of NO. For instance NO can alter the function of enzymes by binding to metal centers. This type of interaction could result in outcomes as disparate as control of blood pressure or death of an invading bacterium. NO can also be readily converted to higher nitrogen oxides such as N_2O_3, NO_2 or ONOOH, which have discrete chemical and biological properties. The ultimate result will depend upon numerous factors, particularly the location and concentration of NO produced. Therefore, site-specific modulation of NO concentration offers intriguing therapeutic possibilities for an expanding list of diseases.

The overall goal of my research is to provide pharmacological therapies for diseases such as cancer, heart failure and stroke. Accomplishing this goal requires both the development of compounds to deliver NO and other nitrogen oxides and a full understanding of the biological consequences of nitrogen oxide production by these compounds. To this end, we are currently engaged in the investigation of the reactivity of nitrogen oxides at the molecular, biomolecular,

systemic and whole organism levels.

Our current projects are designed to answer questions of potential medical importance through a multi-disciplinary approach, including analytical, synthetic, inorganic and biochemical techniques. The project categories include:

1. development and utilization of analytical techniques for detection and measurement of NO and other nitrogen oxides as well as the resultant chemistry of these species

2. synthesis of potential donors of NO and other nitrogen oxides

3. chemical characterization of these compounds (spectroscopic features, kinetics, mechanisms and profiles of nitrogen oxide release, etc.)

4. biological characterization of these compounds (assay of effects on biological compounds, mechanisms and pathways, *in vitro* determination of potential for therapeutic utility, etc.)

5. identification of potential targets, such as enzymes, for treatment of disease through exposure to nitrogen oxide donors

Selected Publications

D.J. Salmon, C.L. Torres de Holding, L. Thomas, K.V. Peterson, G.P. Goodman, J.E. Saavedra, A.Srinivansan, K.M. Davies, L.K. Keefer, K.M. Miranda. "HNO and NO release from a primary amine-based diazeniumdiolate as a function of PH." *Inorg. Chem.*, 50, 3262-3270 (2011).

D. Andrei, D.J. Salmon, S. Donzelli, A. Wahab, J.R. Klose, M.L. Cintro, J.E. Saavedra, D.A. Wink, K.M. Miranda, L.K. Keefer. "Dual mechanisms of HNO generation by a nitroxyl prodrug of the diazeniumdiolate (NONOate) class." *J. Am. Chem. Soc.*, 132, 16526-16532 (2010).

M.R. Kumar, J.M. Fukuto, K.M. Miranda, P.J. Farmer. "Reactions of HNO with heme proteins: new routes to HNO-heme complexes and insight into physiological effects." *Inorg. Chem.*, 49, 6283-6292 (2010).

T.W. Miller, M.E. Cherney, N.Franco, P.J. Farmer, S.B. King, A.J. Hobbs, K.M. Miranda, J.N. Burstyn, J.M. Fukuto. "The effects of nitroxyl (HNO) on soluble guanylate cyclase activity: interactions at ferrous heme and cysteine thiols." *J. Biol. Chem*, 284, 21788-21796 (2009).

S. Donzelli, M.G. Espey, W. Flores-Santana, C.H. Switzer, G.C. Yeh, J. Huang, D. Stuehr, S.B. King, K.M. Miranda, D.A. Wink. "Generation of nitroxyl by heme protein-mediated peroxidation of hydroxylamine but not N-hydroxy-L-arginine." *Free Radic. Biol. Med.*, 45, 578-584 (2008).

A.S. Dutton, C.P. Suhrada, K.M. Miranda, D.A. Wink, J.M. Fukuto, K.N. Houlk. "Mechanism of pH dependent decomposition of monoalkylamine diazeniumdiolates to form HNO and NO, deduced from Density Functional Theory and CBS-QB3 calculations." *Inorg. Chem.*, 45, 2448-2456 (2006).

S. Donzelli, M.G. Espey, D.D. Thomas, D. Mancardi, C.G. Tocchetti, L.A. Ridnour, N. Paolocci, S.B. King, K.M. Miranda, G. Lazzarino, J.M. Fukuto, D.A. Wink. "Discriminating formation of HNO from other reactive nitrogen oxide species." *Free Radic. Biol. Med.*, 40, 1056-1066 (2006).

K.M. Miranda, T. Katori, C.L. Torres de Holding, L. Thomas, L.A. Ridnour, W.J. McLendon, A.S. Dutton, H.C. Champion, D. Mancardi, C.G. Tocchetti, J. Saavedra, L.K. Keefer, K.N. Houk, J.M. Fukuto, D.A. Kass, N. Paolocci, D.A. Wink. "Comparison of the NO and HNO donating properties of diazeniumdiaolates. Primary amine adducts release HNO in vivo." *J. Med. Chem.*, 48, 8220-8228 (2005).

K.M. Miranda, H. Nagasawa, J. Toscano. "Donors of HNO." *Curr. Topics Med. Chem.*, 5, 649-664 (2005).

K.M. Miranda, A.S. Dutton, L.A. Ridnour, C.A. Foreman, E. Ford, N. Paolocci, T. Katori, D. Mancardi, D.D. Thomas, M.G. Espey, K.N. Houk, J.M. Fukuto, D.A. Wink. "Mechanism of aerobic decomposition of Angeli's salt at physiological pH." *J. Am. Chem. Soc.*, 127, 722-731 (2005).

K.M. Miranda. "The chemistry of niroxyl (HNO) and implications in biology." *Coordin. Chem. Rev.*, 249, 433-455 (2005).

K.M. Miranda, N. Paolocci, T. Katori, D.D. Thomas, M.D. Bartberger, M.G. Espey, D.A. Kass, M. Feelisch, J.M. Fukuto, D.A. Wink. "A biochemical rationale for the orthogonal behavior of nitroxyl and nitric oxide in the cardiovascular system." *Proc. Natl. Acad. Sci. USA*, 100, 9196-9201 (2003).

N. Paolocci, T. Katori, H.C. Champion, M.E. St. John, K.M. Miranda, J.M. Fukuto, D.A. Wink, D.A. Kass. "Positive inotropic and lusitropic effects of HNO/NO in failing hearts; independence from ß-

adrenergic signaling." *Proc. Natl. Acad. Sci. USA*, 100, 5537-5542 (2003).

K.M. Miranda, R.W. Nims, D.D. Thomas, M.G. Espey, D. Citrin, M.D. Bartberger, N. Paolocci, J.M. Fukuto, M. Feelisch, A. Wink. "Comparison of the reactivity of nitric oxide and nitroxyl with heme proteins. A chemical discussion of the differential biological effects of these redox related products of NOS." *J. Inorg. Biochem.*, 93, 52-60 (2003).

N. Paolocci, W.F. Saavedra, K.M. Miranda, C. Martignani, T. Isoda, J.M. Hare, M.G. Espey, J.M. Fukuto, M. Feelisch, D.A. Wink, D.A. Kass. "Nitroxyl anion exerts redox-sensitive positive cardiac inotropy *in vivo* by calcitonin gene related peptide signaling." *Proc. Natl. Acad. Sci. USA*, 98, 10463-10468 (2001).

K.M. Miranda, M.G. Espey, D.A. Wink. "A rapid, simple spectrophotometric method for detection of nitrate and nitrite." *Nitric Oxide*, 5, 96-71 (2001), cover feature.

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